REMARKS/ARGUMENTS

1. The Rejection under 102(e)

Claims 1, 6, and 8 through 10 remain rejected under 35 USC 102(e) as being directed to subject matter assertedly anticipated by the disclosure of Stinchcomb, et al., US Patent 5,877,021 ("the '021 patent") for reasons set out in the previous office action. In brief, the examiner asserted (i) the invention in the '021 patent is directed to nucleic acid-based techniques which include, *inter alia,* ribozymes and antisense nucleic acids [office action (OA), p. 2]; (ii) the invention in the '021 patent includes methods to treat, *inter alia,* autoimmune disorders [OA, p. 2], and in particular psoriasis [OA, p. 3], and to inhibit synthesis of B7-1, B7-2, B7-3 and CD40 proteins [OA, p. 2]; (iii) the invention in the '021 patent describes topical administration of compounds of the invention [OA, p. 3]; and (iv) "the instant claims are directed to antisense sense compounds, [and] one of skill in the art would immediately recognize that ribozymes are a form of antisense compound since it hybridizes to the target nucleic acid in an antisense manner"[OA, p.3]. The applicants respectfully disagree.

Contrary to the examiner's assertion, ribozymes are not simply a form of antisense and to the extent that the '021 patent provides guidance for making and using any invention, it is limited only to ribozymes. Because the '021 patent is essentially unrelated to antisense technology, and a reference under 102 must be enabling for subject matter of claims the reference purportedly anticipates, the '021 patent disclosure cannot anticipate antisense compounds or methods of their use.

"A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354, 65 USPQ2d 1385, 1416 (Fed. Cir. 2003). *See Bristol-Myers Squibb v. Ben Venue Laboratories, Inc.*, 246 F.3d 1368, 1374, 58 USPQ2d 1508, 1512 (Fed. Cir. 2001) ("To anticipate the reference must also enable one of skill in the art to make and use the claimed invention."); *PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1566, 37 USPQ2d 1618, 1624 (Fed. Cir. 1996) ("To anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter."). The principles underlying application of the

criteria of enablement to the content of the prior art were discussed in *In re Donohue*, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985):

> It is well settled that prior art under 35 U.S.C. §102(b) must sufficiently describe the claimed invention to have placed the public in possession of it. Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his own knowledge to make the claimed invention. Accordingly, even if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it is not enabling. It is not, however, necessary that an invention disclosed in a publication shall have actually been made in order to satisfy the enablement requirement.

Id. at 533, 226 USPQ at 621. *See also In re Borst*, 345 F.2d 851, 855, 145 USPQ 554, 557 (CCPA 1962) ("the disclosure must be such as will give possession of the invention to the person of ordinary skill. Even the act of publication or the fiction of constructive reduction to practice will not suffice if the disclosure does not meet this standard.").

Enablement requires that "the prior art reference must teach one of ordinary skill in the art to make or carry out the claimed invention without undue experimentation." *Minnesota Mining and Manufacturing Co. v. Chemque, Inc.*, 303 F.3d 1294, 1301, 64 USPQ2d 1270, 1278 (Fed. Cir. 2002). The factual premises of the enablement analysis for biological processes were addressed in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), the court explaining that determination of whether the requisite amount of experimentation is undue may include consideration of (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id. at 737; 8 USPQ2d at 1404. All of the *Wands* factors need not be reviewed when determining whether a disclosure is enabling. *See Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213, 18 U.S.P.Q.2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts.").

In arts such as chemistry and biotechnology, enablement requires more extensive disclosure because of the unpredictability involved in practicing inventions in these arts. *See generally* 2 Donald S. Chisum, *Chisum on Patents,* §7.03[4][d][i], at 7-58 (1999) ("A recurring problem is whether a specification that sets forth a single or limited number of examples can be enabling of broad claims when the subject matter concerns biological materials or reactions, which are generally considered to be unpredictable.") and cases cited therein; *Ex parte Hitzeman*, 9 USPQ2d 1821 (Bd. Pat. App. Interf. 1988) ("In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more is required....").

Where the teachings set forth in the specification provide no more than a "plan" or "invitation" for those of skill in the art to experiment practicing the claimed invention in species other than that disclosed in the specification, they do not provide sufficient guidance or specificity as to how to execute that plan. *See Fiers v. Revel*, 984 F.2d 1164, 1171, 25 U.S.P.Q.2d 1601, 1606 (Fed. Cir. 1993); *Wright*, 999 F.2d at 1562, 27 U.S.P.Q.2d at 1514. The Federal Circuit has stated,

> Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.

Genentech v. Novo Nordisk, 108 F.3d 1361, 1366, 42 U.S.P.Q.2d 1001, 1005 (Fed. Cir. 1997).

The examiner's position that the '021 patent discloses that antisense is part of the '021 patent invention is correct, but any assumption that all the patent discloses regarding ribozymes is equally applicable for making and using antisense is unsupported. The specification teaches that antisense molecules and ribozymes are distinct classes of compounds and is devoted, except for the passing reference to antisense in general, entirely to making and using ribozymes.

At page 2 of the office action, the examiner correctly notes that enzymatic nucleic acid molecules are ribozymes, but it is the applicant's position that ribozymes are not simply a form of antisense compounds. Enzymatic compounds specifically cleave a target RNA [*see* Col. 6, lines 24-30 in the '021 patent] while antisense compounds *lack enzymatic activity* [Col. 6, lines 39-44]. The mechanisms by which these two types of compounds inhibit expression of a target are therefore not the same.

The examiner's statement that an enzymatic nucleic acid (ribozyme) includes a region of that hybridizes to a target [OA, p. 3] ignores the fact that this class of compounds also includes a catalytic site that *does not hybridize to the target*. The catalytic site in a ribozyme includes a degree of secondary structure [*see, e.g.*, Figs. 1, 2, 3, 4 and 5 in the '021 patent] that is not found in functional antisense, and because of this secondary structure, the catalytic site is not complementary to target sequences and cannot hybridize to a target nucleic acid. Ribozymes are therefore *only in part* complementary to a target. An antisense molecule, on the other hand, has no such catalytic region [*see* Col. 6, lines 39-44] and hybridizes to the target over its entire length, depending on the degree of complementarity. Ribozymes and antisense are therefore chemically and structurally distinguishable.

Despite the mechanistic, chemical and structural differences between enzymatic and non-enzymatic nucleic acids, the examiner implies without evidence that disclosure in the '021 patent explicitly relating to use of ribozymes also applies to use of antisense. For example, the examiner alleges that the '021 patent discloses that "administration of the compositions of the invention... may include, among others, ***topicals*** (col. 12, lines 18-36)." [Emphasis in original.] To the extent that this comment is relevant to subject matter of the rejected claims, it must be assumed that the examiner is asserting that "the antisense composition of the invention" can be delivered topically. The paragraph to which the examiner refers, however, states,

> Sullivan, et al., supra, describes the general methods for delivery of ***enzymatic RNA molecules. Ribozymes*** may be administered to cells by a variety of methods known to those familiar to the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as hydrogels, cyclodextrins, biodegradable nanocapsules, and bioadhesive microspheres. For some

> indications, ***ribozymes*** may be directly delivered ex vivo to cells or tissues with or without the aforementioned vehicles. Alternatively, the RNA/vehicle combination is locally delivered by direct injection or by use of a catheter, infusion pump or stent. Other routes of delivery include, but are not limited to, intravascular, intramuscular, subcutaneous or joint injection, aerosol inhalation, oral (tablet or pill form), topical, systemic, ocular, intraperitoneal and/or intrathecal delivery. More detailed descriptions of ***ribozyme delivery*** and administration are provided in Sullivan et al., supra and Draper et al., supra which have been incorporated by reference herein. [Emphasis added.]

This citation is found in a section which begins at col. 10, line 14, entitled "RIBOZYMES," and a subsection which begins at col. 11, line 64, entitled "Optimizing Ribozyme Activity." When properly read in context, therefore, the referenced disclosure explicitly relates only to delivery of ribozymes. If it is the examiner's position that ribozymes and antisense can effectively be delivered in the same manner, the examiner has provided no factual evidence which backs this position.

To the extent that the '021 is enabling for any subject matter, it is limited to ribozymes. The '021 specification includes description of characteristics of the claimed ribozymes [*see*, for example, Table I at Col. 15] but there is no description of any characteristic of any antisense compound. The '021 disclosure provides specific sequences of various ribozyme embodiments [*see, e.g.*, Table II beginning at Col. 16 and Table III beginning at Col. 20], but, again, none for any antisense compound. Significantly, there is no teaching, guidance or working example in the '021 patent that *any* of the disclosed ribozymes are in fact useful for inhibiting specific protein expression *in vitro*, much less for *in vivo* topical treatment of any condition associated with specific protein expression. The same disclosure is missing for any antisense compound.

Patent applications relating specifically to antisense technology have been found to lack enablement while including considerably more disclosure than this. For example, in *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 52 U.S.P.Q.2d 1129 (Fed. Cir. 1999), the Federal Circuit affirmed the district court's holding that patent claims directed

to the practice of antisense technology in all types of cells were not enabled by the specification which disclosed three working examples of use of such technology only in *E. coli* cells ("the specifications provided virtually no disclosure of the practice of antisense in cells other than *E. coli*. We conclude, therefore, that the breadth of enablement in the patent specifications is not commensurate in scope with the claims, as the quantity of experimentation required to practice antisense in cells other than *E. coli* at the filing date would have been undue." *Enzo*, 188 F.3d at 1377, 52 U.S.P.Q.2d at 1140). The court upheld the lower court decision that the claims were not enabled in view of relevant *Wands* factors, stating that antisense technology was unpredictable and that the quantity of experimentation that would be required to practice the method in cells other than *E. coli* would have been undue. [*Id.* at 1140, 188 F.3d at 1377] More specifically, the district court found that the claims embraced practice of the claimed method in "the entire universe of cells," which the court described to be "infinite." [*Id.* at 1136, 188 F.3d at 1372] The lower court had agreed with evidence that the disclosed methods were not universally applicable or as easy to apply as was initially hoped, and concluded the art was unpredictable. Despite a high level of skill in the art, the court found that the amount of experimentation required to practice the invention "was quite high" [*Id.*] and direction provided by the limited number of *three* working examples was "very narrow" [*Id.* at 1138, 188 F.3d at 1374], particularly in view of the other *Wands* factors considered. This minimal disclosure "constituted no more than a plan or invitation to practice antisense in those [non-*E. coli*] cells." [*Id.* at 1138, 188 F.3d at 1375] An analysis of the *Wands* factors as they apply to the presently rejected claims, in view of the facts in *Enzo,* must lead to the same conclusion.

Since the Federal Circuit found it to be so in the 1999 *Enzo* case, it can be assumed that the level of skill in the antisense art is high. Also as evidenced by *Enzo*, the courts have found that biotechnology arts in general are unpredictable. (*See also Ex parte Hitzeman*, 9 USPQ2d 1821 (Bd. Pat. App. Interf. 1988).) As demonstrated in the applicants' specification, synthesis and identification of functional antisense molecules (of which the specification provides a multitude of examples) require a large quantity of experimentation. As discussed above, the '021 patent provides no guidance for making or actually using *any* antisense compounds and there are no working examples in the '021 patent using *any* RNA technology. Regardless of other W*ands* factors, the limited guidance and working examples

in the cited '021 patent, as was the case in *Enzo*, must lead to the conclusion that making and using the presently claimed antisense invention cannot be accomplished following the teaching of the '021 patent without undue experimentation.

Previously, the applicants have argued that the '021 patent makes only passing reference to antisense compounds, and nothing the examiner has argued changes this position. The disclosure in the '021 patent as it relates to antisense is at best a "germ" of an idea which does nothing more than invite the person of skill in the art to attempt to practice the antisense invention of the rejected claims. This passing reference is not an enabling disclosure and as such, the limited disclosure of the '021 patent cannot anticipate the subject matter of claims 1, 6, and 8 through 10. Accordingly, the rejection must be withdrawn.

2. <u>The 103 Rejection</u>

Claims 1 through 14 were rejected under 35 USC 103(a) as being directed to subject matter assertedly rendered obvious by the disclosure of the '021 patent or Freeman, *et al.* US Patent No. 5,942,607 ("the '607 patent"), "either in view of Abramowicz (WO 94/17773) and Cooper (WO 93/24134 A1)." The '021 patent was cited for purportedly disclosing nucleic acid-based techniques including, *inter alia,* antisense for treating autoimmune conditions such as psoriasis by inhibiting B7 protein synthesis [OA, p. 8]. The examiner asserted that the '021 patent also teaches delivery of "nucleic acid inhibitors" via topical means [OA, p. 9]. The '607 patent was cited for assertedly teaching (i) use of antisense to inhibit B7 protein expression, (ii) two specific antisense inhibitors, and (iii) treatment of autoimmune disorders [OA, p. 9]. Abramowicz was cited for disclosing inhibition of B7 in treatment of atopic dermatitis and chronic eczema [OA, p. 10]. Cooper was cited for disclosing treatment of cellular hyperproliferation, including psoriasis, chronic dermatitis, psoriasiform dermatitis and atopic dermatitis, using IL-1 antisense oligonucleotides 8 to 40 bases in length with various modifications [OA, p. 10-11] From these disclosures the examiner asserted it would have been obvious to modify the disclosures of the '021 and '607 patents to provide (i) the presently claimed pharmaceutical compositions and (ii) methods for topically treating inflammatory skin diseases using modified

oligonucleotides 8 to 30 bases in length as described in Cooper. The examiner asserted that the motivation to modify the references arises from Coopers teaching that modified oligonucleotides are more stable and that Cooper "provides motivation and an expectation of success for the treatment of various inflammatory skin disorders including dermatitis and psoriasis." [OA, p. 11]. The examiner also asserted that motivation to modify the '021 and '607 patents to provide methods to treat specific conditions arises from Abramowicz [OA, p. 11-12]. Motivation to modify disclosure of the patents to provide pharmaceutical compositions for treatment of specific conditions was also asserted to arise from Abramowicz. [OA, p. 12]

The applicants respectfully disagree. The claimed subject matter *as a whole* is not suggested by the combined disclosures relied on by the examiner and nothing in these disclosures suggests that the primary references can or should be modified to provide the invention as claimed. Moreover, the combined disclosures fail to describe any *in vivo* application of antisense technology, thereby precluding any assertion that the worker of skill in the art would have any expectation of success in carrying out the claimed methods or producing the claimed pharmaceutical composition having any utility. This failure to provide guidance for *in vivo* administration of antisense as claimed also precludes the combined disclosures of the references from enabling the worker of skill in the art to make and use the invention as claimed.

A claimed invention is unpatentable due to obviousness if the differences between it and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a). In order to determine obviousness as a legal matter, four factual inquiries must be made concerning: 1) the scope and content of the prior art; 2) the level of ordinary skill in the art; 3) the differences between the claimed invention and the prior art; and 4) secondary considerations of nonobviousness, which in case law is often said to include commercial success, long-felt but unresolved need, failure of others, copying, and unexpected results. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966); *Miles Labs., Inc. v. Shandon, Inc.*, 997 F.2d 870, 877, 27 USPQ2d 1123, 1128 (Fed. Cir. 1993). The consistent criterion for determination of obviousness is whether the prior art would have

suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in light of the prior art. *In re Dow Chemical Co.* 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir 1988) (citing *Burlington Industries v. Quigg*, 822 F.2d 1581, 1583, 3 USPQ2d 1436, 1438 (Fed. Cir. 1987); *In re Hedges*, 783 F.2d 1038, 1041, 228 USPQ 685,687 (Fed. Cir. 1986); *Orthopedic Equipment Co.* v. *United States*, 702 F.2d 1005, 1013, 217 USPQ 193, 200 (Fed. Cir. 1983); *In re Rinehart* 531 F.2d 1048, 1053-54, 189 USPQ 143, 148 (CCPA 1976)). Both the suggestion and the expectation of success must be found in the prior art, not the applicant's disclosure. *Id.* Moreover, and significant with the instant facts, in order to render a claimed apparatus or method obvious, the prior art must enable one skilled in the art to make and use the apparatus or method. *See Motorola, Inc., v. Interdigital Technology Corporation*, 121 F.3d 1461, 1471; 43 U.S.P.Q.2D (BNA) 1481, 1489 (Fed Cir. 1997) (quoting *Beckman Instruments, Inc. v. LKB Produkter AB*, 892 F.2d 1547, 1551, 13 U.S.P.Q.2D (BNA) 1301, 1304 (Fed. Cir. 1989)). The legal standard for enablement is set forth above with respect to the §102 rejection.

The first step in an obviousness analysis is a determination of the scope of and content of the prior art. As discussed above in detail, the '021 patent is unrelated to antisense therapy. In brief, with the exception of a simple comment that the invention embraces antisense, everything in the disclosure is related to ribozyme technology. As pointed out above, antisense and ribozymes are distinct classes of compounds and any assertion that the disclosure as it relates to ribozymes in also applicable to antisense is unsupported factually. Accordingly, reference in the patent to topical administration of a ribozyme cannot necessarily be extrapolated to embrace topical administration of antisense. Moreover, even if this extrapolation is made, the patent does not teach successful, *i.e.*, useful, administration using either ribozymes or antisense in any topical pharmaceutical composition.

The '607 patent provides polynucleotides encoding B7 polypeptides and discloses two specific antisense molecules - one proposed to inhibit the function of B7-1 and the other proposed to inhibit B7-2 - which the patent generically discloses can be "administered to a patient to prevent the synthesis" of B7 proteins. [Col 12, lines 36-44] The patent does not, however, disclose or suggest actual topical administration of either molecule

to a patient. Moreover, the patent does not demonstrate that the disclosed antisense molecules have any inhibitory effect on B7 synthesis or function.

Abramowicz describes use of compositions comprising IL-10 and results from use of such compositions. The publication discloses that IL-10 is an inhibitor of B7 and describes cell culture experiments wherein IL-10 is able to inhibit B7-dependent IL-5 production. As with the '021 and '607 patents, Abramowicz provides no guidance relating to topical *in vivo* administration of any B7 inhibitor. Likewise, Cooper describes experimental work with IL-1 antisense that is carried out solely in cell culture. While Cooper includes claims to methods of treating hyperproliferation of skin or epithelial cell, the publication provides no indication how to carry out topical administration or even if such a route of administration would work.

For the second step in the analysis, it is assumed that the level of skill in the art is high.

In the third step, the difference between the claimed invention and the art is determined. The rejected claims are directed to two aspects of the invention; the first being a proven method for treating an inflammatory skin disorder using topical administration of antisense directed to a B7-encoding polynucleotide, and the second a pharmaceutical composition useful for such a method. As discussed above, the '021 patent disclosure does not disclose any actual methods for topical administration of ribozymes or antisense. Nothing in the '607 patent, Abramowicz and/or Cooper demonstrates use of any topical therapeutics or any pharmaceutical compositions useful in topical administration. On top of the absence in the cited references of a working method or useful composition as presently claimed, the combined disclosures of all of the references also lack express, implied or prophetic disclosure of any of the specifics, *i.e.,* antisense concentrations and additives in a pharmaceutical composition, dosages and regimens for topical administration, *etc.*, necessary to make and use the claimed topical methods and compositions. Without any specifics for practice of the claimed invention, the differences between the prior art and the claimed subject matter must be considered significant because the present specification actually demonstrates in Example 21 successful use of the claimed topical methods and compositions *in vivo*.

Whatever motivation to make the invention as claimed that the worker of skill would derive from the combination of the references is counterbalanced by the any expectation of success on the part of the skilled worker derived from the same references. As pointed out above, none of the cited references provide a working example of topical *in vivo* practice for any aspect of the claimed invention and this omission alone casts doubt on any assertion that the worker of skill could derive any reasonable expectation of success from the cited art to make the claimed invention. Only the disclosure of Cooper suggests that any inhibitory effect using antisense, but the results are limited to interleukin-1 in an *in vitro* environment. Cooper does not suggest and disclose that the system described is an accepted model useful for predicting topical therapeutic benefit or that observations using the system were ever corroborated with later demonstrated benefit. While the combined disclosures may arguably invite the skilled worker to attempt to make the presently claimed invention, the disclosures offer nothing that would provide the worker with any expectation that the invention would be useful.

Finally, for reasons discussed above relating to the rejection under §102 with regard to failure of the disclosure of the '021 patent to enable the invention as claimed, the same holds true for the combined disclosures cited by the examiner to assertedly support the rejection under §103. None of the cited provides any working example of topical *in vivo* administration of any antisense molecule resulting in a therapeutic benefit. The difference between what is disclosed in the combined art is therefore so great that, even if the cited disclosures actually suggested the present invention, the suggestion would amount to nothing more than an invitation for experimentation. As above, such an invitation or "germ" of an idea is insufficient to enable the worker of skill in the art to make and use the present invention without undue experimentation.

The applicants submit that the combination of disclosures cited by the examiner is so far removed from the claimed invention that the combination cannot suggest or enable the invention as claimed. The cited art is simply devoid of any evidence that antisense is useful (*i.e.,* will actually work) in a topical *in vivo* environment. Absent this teaching in the art, motivation on the part of the skilled worker to modify the art to make the claimed invention is outweighed by the total absence of any disclosure that would provide the

skilled worker with a reasonable expectation of success. Moreover, even if so motivated, the skilled worker would not be able to practice the invention without undue experimentation. Accordingly, the rejection of all claims under 103(a) must also be withdrawn.

3. Conclusion

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. According, the Examiner is respectfully requested to pass this application to issue.

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Respectfully submitted,

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